

# Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria

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**On behalf of the International Myeloma Working Group**

# Smoldering multiple myeloma

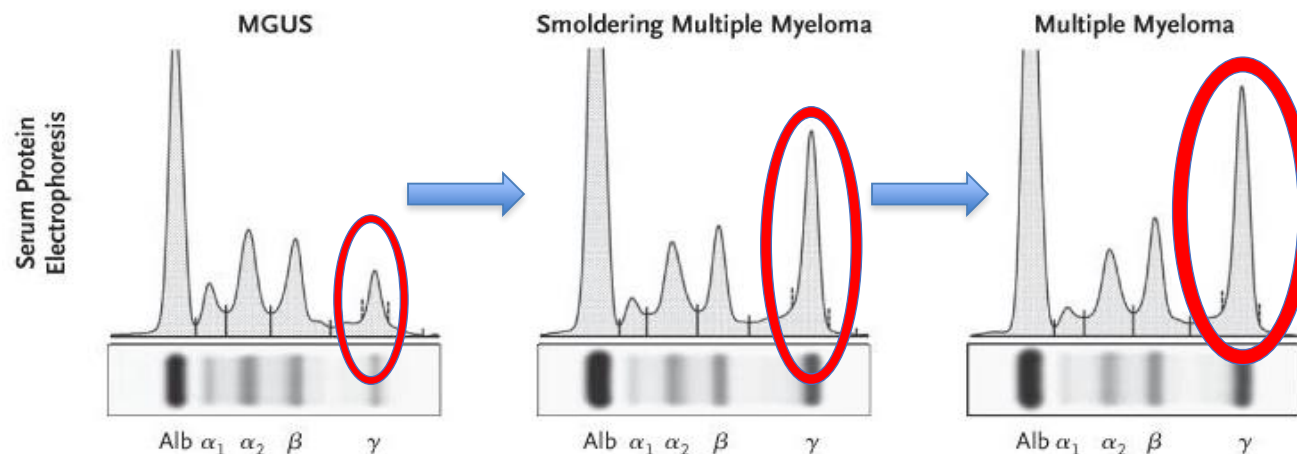
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## SMOLDERING MULTIPLE MYELOMA

ROBERT A. KYLE, M.D.,  
AND PHILIP R. GREIPP, M.D.

**M**ULTIPLE myeloma is characterized by an increase of abnormal plasma cells in the bone marrow and monoclonal protein in the serum, often with osteolytic bone lesions. Its course is progressive: anemia, weakness, fatigue, fractures, bone pain, hypercalcemia, renal insufficiency, recurrent infections, bleeding, and deterioration lead to death. However, we have seen six patients with illnesses that met the criteria for the diagnosis of multiple myeloma<sup>1</sup> but have not had a progressive course. Although no chemotherapy was given, their condition has remained stable for five or more years. We designate these cases as “smoldering multiple myeloma.” We wish to call attention to this group because smoldering multiple myeloma should be recognized, and treatment withheld.

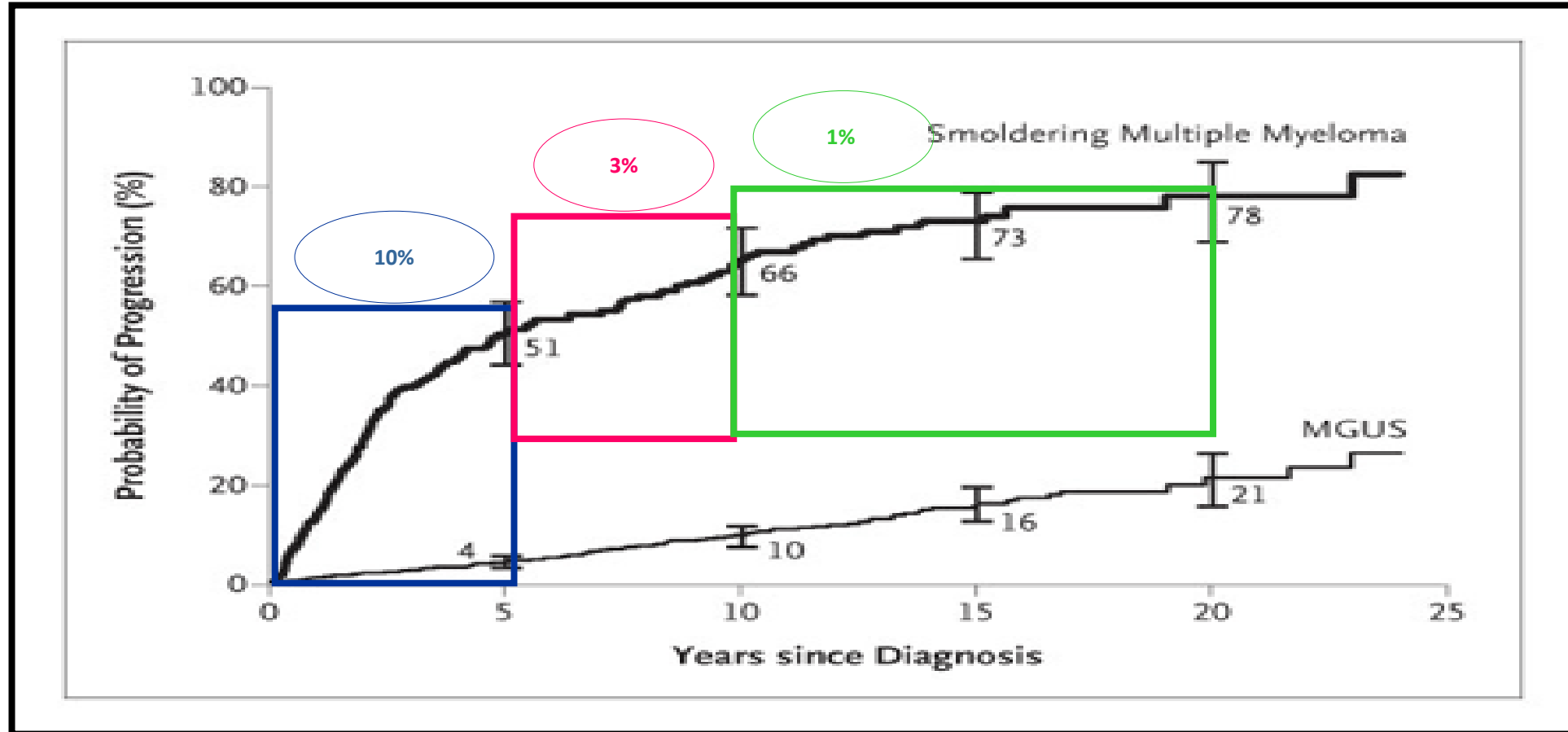


**Increasing levels of monoclonal protein**

**Increasing marrow plasma cell percentage**

**Development of End Organ Damage**

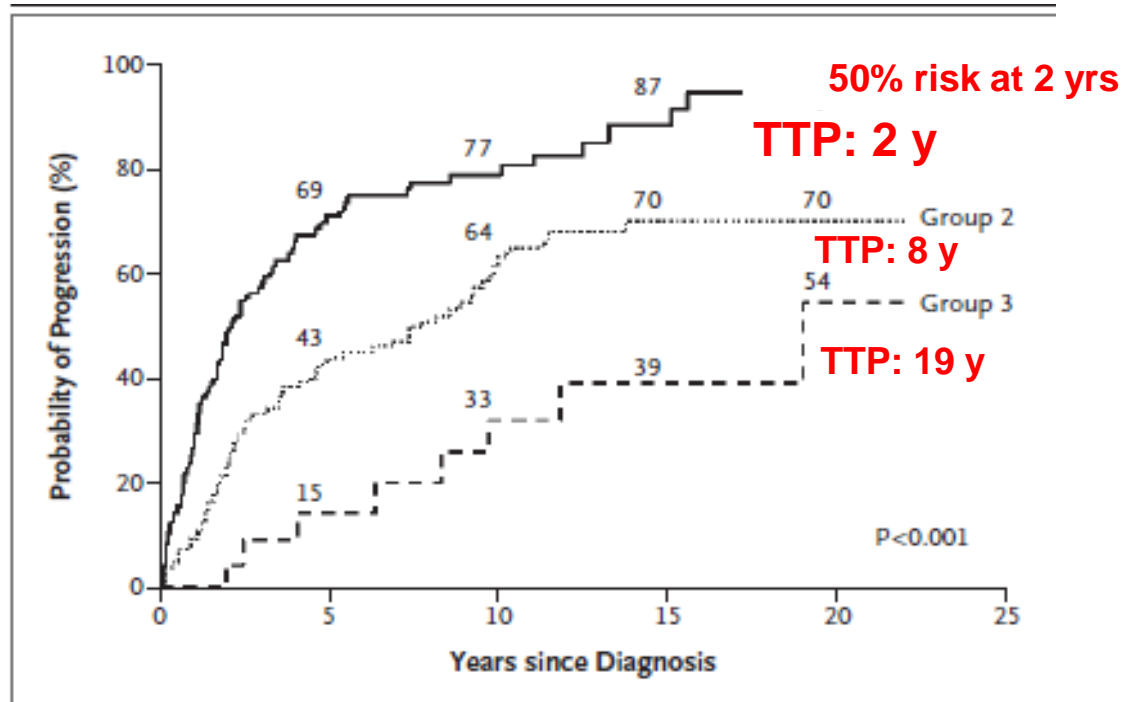
# SMM: heterogeneous disease



# Current models for risk assessment

## Mayo risk model

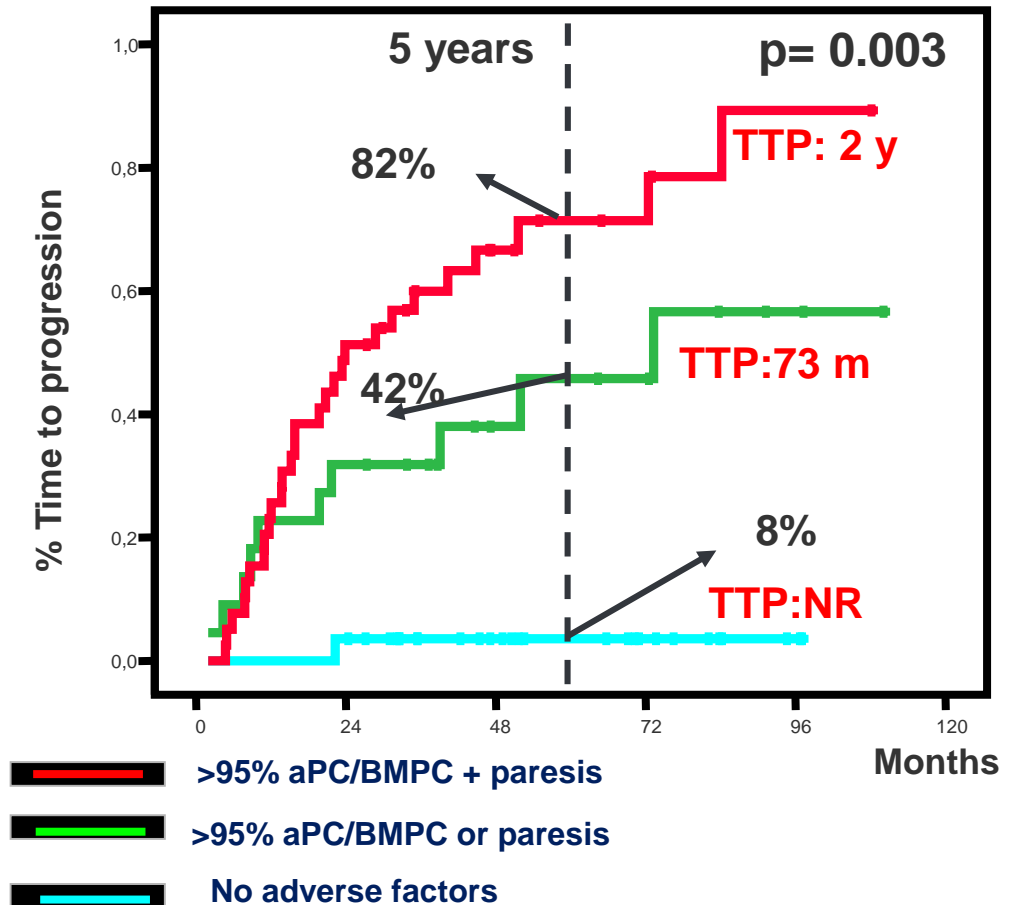
PCs BM infiltration and  
Serum M-component level



Group 1: PCBM ≥ 10% + MC ≥ 3g/dl  
Group 2: PCBM ≥ 10% + MC < 3g/dl  
Group 3: PCBM < 10% + MC ≥ 3g/dl

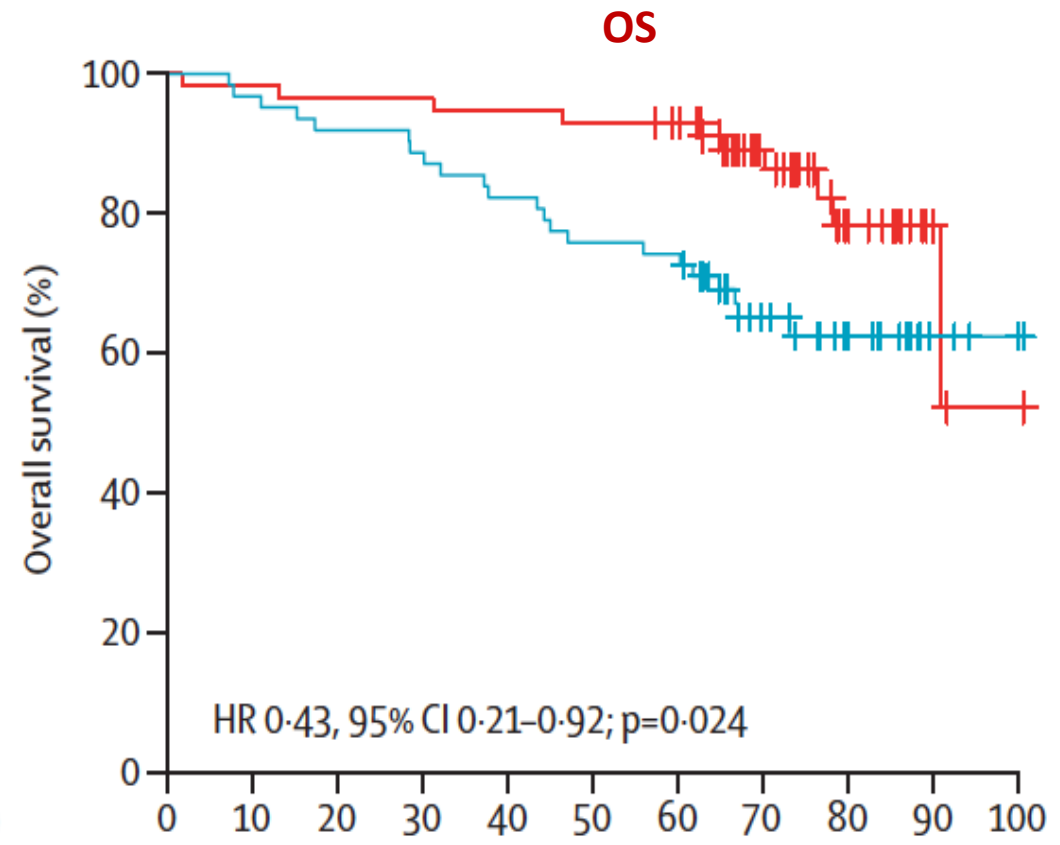
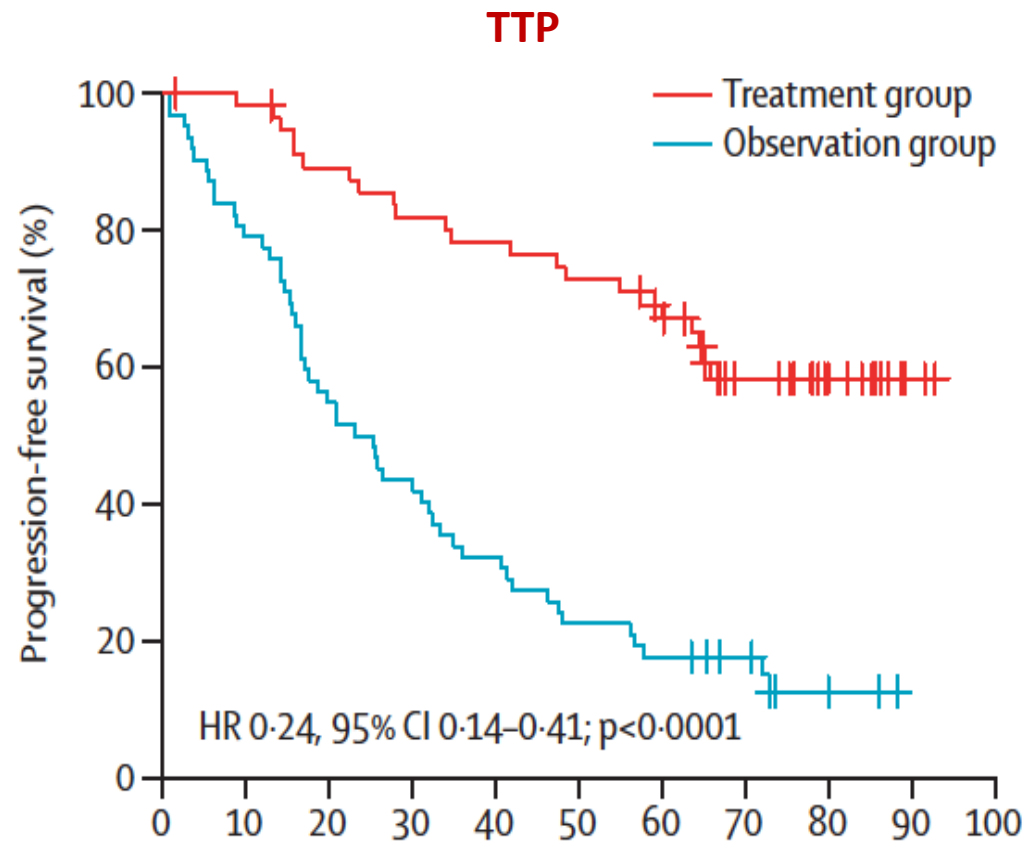
## Spanish model:

Aberrant PCs by immunophenotype plus immunoparesis

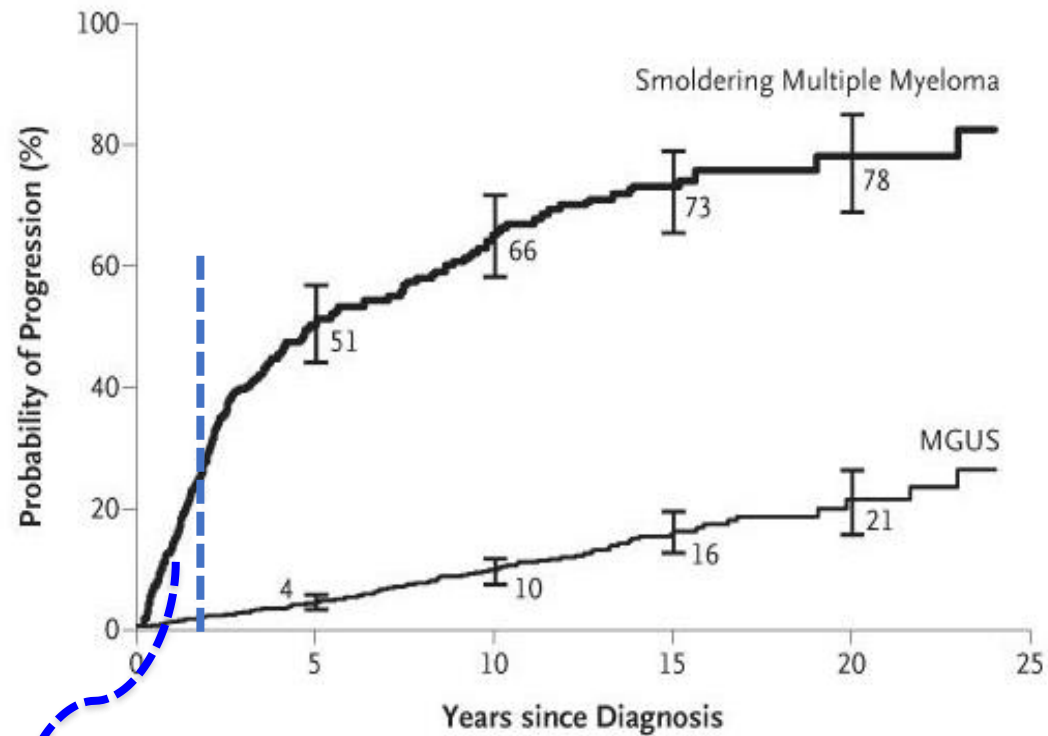


# Spanish and Mayo models were validated in a phase 3 clinical trial

QuiRedex phase 3 trial: Rd vs observation in **high-risk** SMM

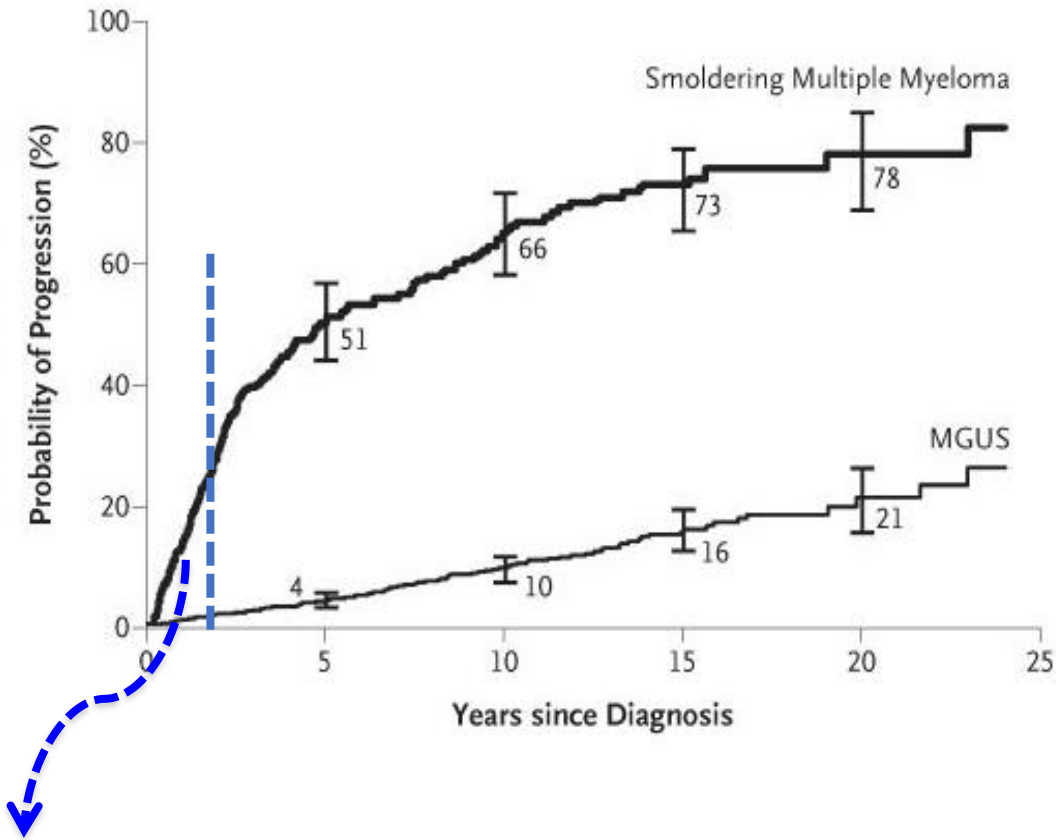


# Redefining MM: A paradigm shift



High risk of progression: Redefine as MM?

# Redefining MM: A paradigm shift



High risk of progression: Redefine as MM?

- HyperCalcemia
- Renal Insufficiency
- Anemia
- Bone Disease
- BMPC  $\geq 60\%$
- $>1$  MRI lesions
- FLC ratio  $> 100$

Predicts an 80% or more risk of progression in 2 years

# Risk stratification in SMM

## Identification of features predicting 50% of progression risk in patients with Smoldering Myeloma

Serum M protein  $\geq 30\text{g/L}$

IgA SMM

Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes

Serum involved/uninvolved FLC ratio  $\geq 8$  (but  $< 100$ )

Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by  $\geq 25\%$  on 2 successive evaluations within a 6-month period)

Clonal BMPCs 50%-60%

Abnormal PC immunophenotype ( $\geq 95\%$  of BMPCs are clonal) and reduction of  $\geq 1$  uninvolved immunoglobulin isotypes

t(4;14) or del(17p) or 1q gain

Increased circulating PCs

MRI with diffuse abnormalities or 1 focal lesion

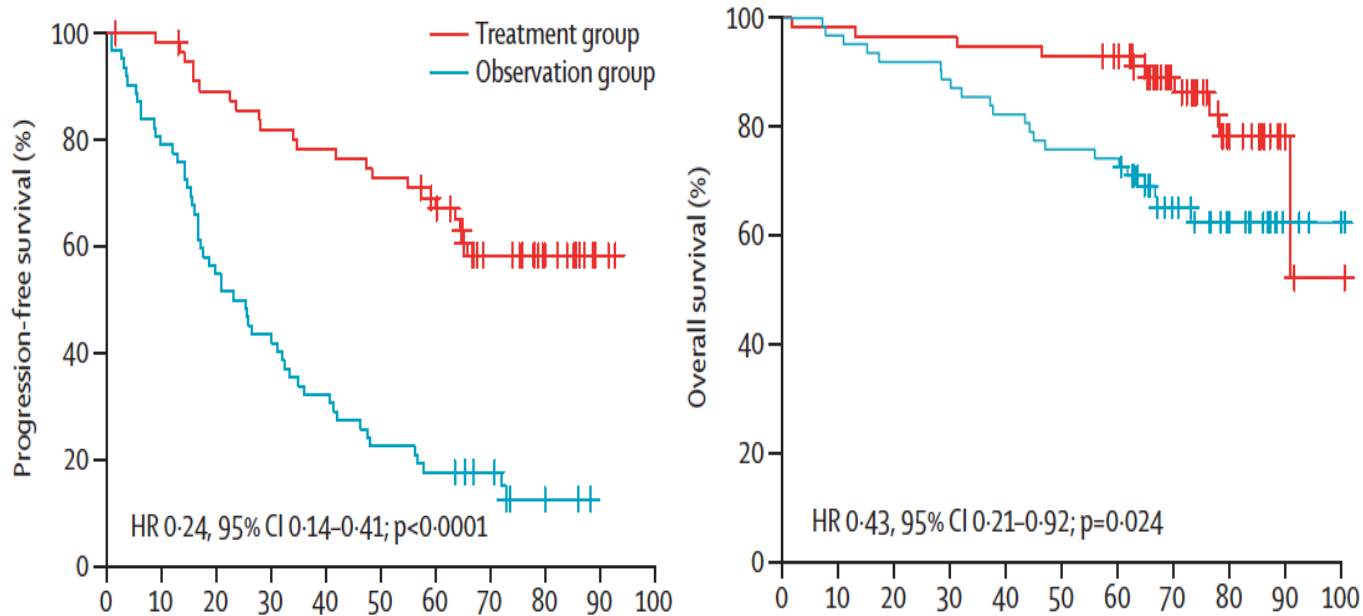
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

- Ongoing trials, irrespective of the model systems used, have targeted a group of patients with a 50% risk of progression at 2 years (approx.) and have shown benefit



# Why is risk stratification important?

QuiRedex phase 3 trial: Rd vs observation in high-risk SMM



E3A06 phase 3 trial: R vs observation in intermediate and high-risk SMM

ECOG Phase trial (E3A06)			
PFS	Len	Obs	HR
1 year	98%	89%	
2 year	93%	76%	
3 year	91%	66%	<b>0.28</b> P<0.001

Spanish Model and Mayo Model identifying only high risk

# Study Design

- **A multicenter, retrospective study of SMM patients diagnosed since January 1, 2004.**
- **Patients were included if:**
  - they had no disease progression within 6 months
  - had baseline data from diagnosis (+/- 3 months)
  - had a follow up of  $\geq 1$  year, and
  - did not participate in a therapeutic trial of SMM.

# Objectives and Methods

- **To identify factors that predicted progression to Myeloma through the evaluation of various clinical and laboratory factors**
- **Univariate Cox regressions** were run for each factor to identify the possible predictors.
- Stepwise regression analysis to fit **multivariable Cox model** and significant risk factors were determined (F-test).
- **Develop a risk score to predict 2-year progression risk**

# Patient characteristics (n=2004)

Characteristic	Number missing	n (%)	Mean (SD)	Median (IQR)	Range
Age (years)	0		63.7 (11.7)	64 (56 - 72)	(26 to 93)
Gender (Male)	0	986 (49.1%)			
Creatinine (mg/dL)	137		0.96 (0.5)	0.88 (0.71 - 1.05)	(0.12 to 9.5)
Albumin (g/dL)	180		4 (0.5)	4 (3.7 - 4.3)	(0.8 to 8.7)
Serum M protein (g/dL)	0		1.9 (1.1)	1.8 (1.1 - 2.6)	(0 to 5)
Heavy chain type					
IgA	123	454 (24.1%)			
IgD		6 (0.3%)			
<b>IgG</b>		<b>1410 (74.8%)</b>			
IgM		16 (0.9%)			
Light chain type,					
<b>Kappa</b>	24	<b>1207 (60.8%)</b>			
Lambda		778 (39.2%)			
Involved to uninvolved FLC ratio	588		34.3 (147.1)	6.4 (2.3 - 24.4)	(0.4 to 3360)
Immunoparesis	240	996 (56.3%)			
Urine M Spike (mg/24hrs)	800		118.5 (858.4)	0 (0 - 30)	(0 to 26390)
BMPC, %	0		19.9 (11.8)	15 (12 - 25)	(0 to 100)
BMPC, higher of biopsy and aspirate %	0		20.7 (11.7)	17 (12 - 25)	(0 to 100)
PET-CT Scan availability	13	374 (18.7%)			
MRI Scan availability	13	709 (35.5%)			

# Identifying prognostic factors

**Univariate Cox regressions** were run for each factor identifying optimal cut-off points followed by a stepwise regression to fit **multivariable Cox model**

Characteristic	Cutpoint	Number missing	HR (95% CI)	P-Value
Age (years)	>57	0	1.42 (1.21, 1.66)	<.0001
Gender (Male)		0	1.12 (0.98, 1.28)	0.1106
Creatinine (mg/dL)	>0.81	136	1.2 (1.04, 1.39)	0.0144
Albumin (g/dL)	>4.09	179	0.72 (0.62, 0.84)	<.0001
<b>Serum M protein (g/dL)</b>	<b>&gt;1.91</b>	<b>0</b>	<b>2.4 (2.09, 2.77)</b>	<b>&lt;.0001</b>
Absolute difference Kappa-Lambda (mg/dL)	>18.54	577	1.55 (1.3, 1.84)	<.0001
Heavy chain type				
IgA		4	0.92 (0.78, 1.09)	0.3336
IgD			N/A	
IgG			Reference	
IgM			N/A	
Light chain type,				
Kappa		24	0.76 (0.66, 0.88)	0.0002
Lambda				
<b>Involved to uninvolved FLC ratio</b>	<b>&gt;19.28</b>	<b>588</b>	<b>2.56 (2.16, 3.05)</b>	<b>&lt;.0001</b>
Immunofixation		65	n/a	
Immunoparesis		238	1.53 (1.31, 1.78)	<.0001
Urine M Spike (mg/24hrs)	>75	797	1.57 (1.28, 1.94)	<.0001
<b>BMPC, %</b>	<b>&gt;16.4</b>	<b>0</b>	<b>2.37 (2.05, 2.74)</b>	<b>&lt;.0001</b>

- Proposed cut-off categories for simplicity:

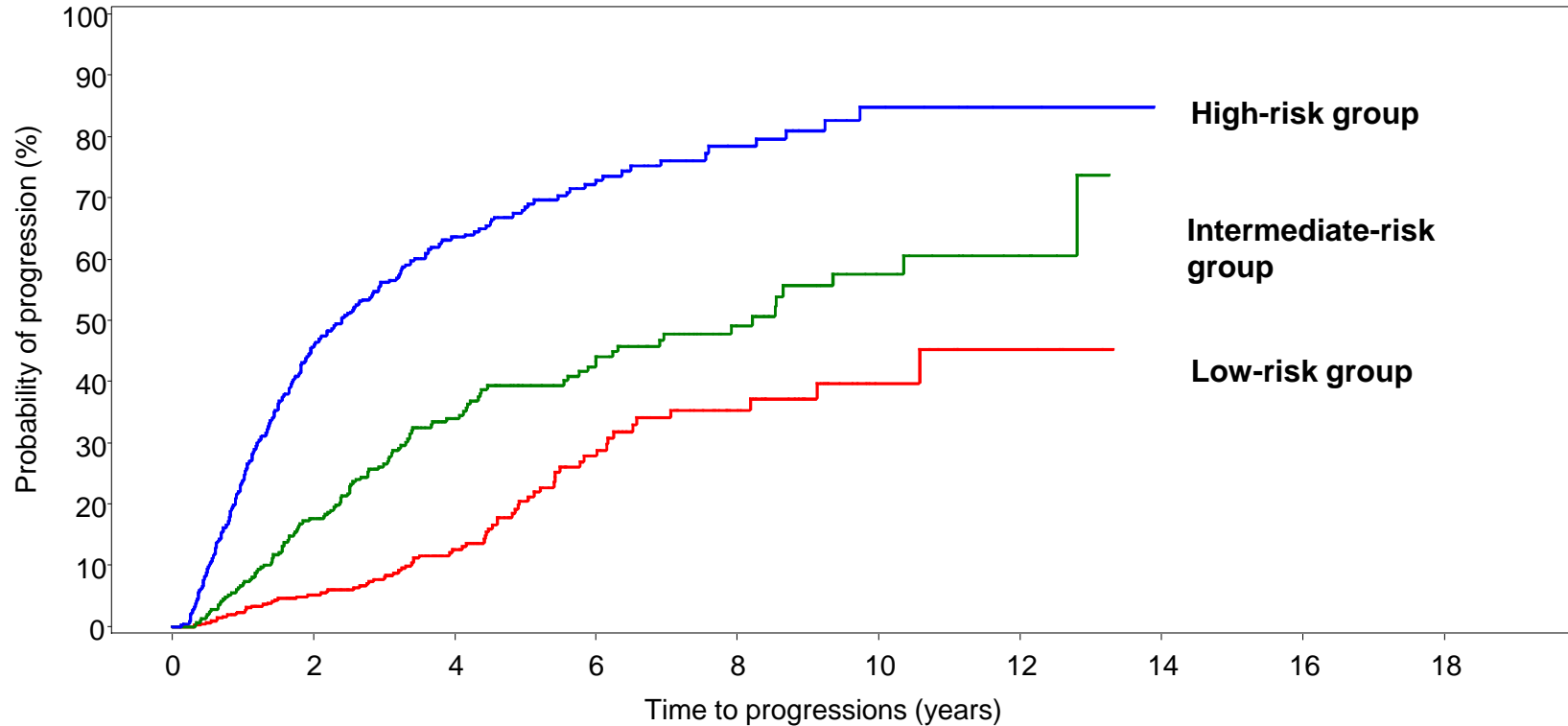
**Serum M Spike: >2 g/dL**

**FLC Ratio: >20**

**BMPC: >20%**

Risk Factor	Hazard Ratio (95% CI) Versus Low-risk group
Serum M Spike (>2 vs ≤2)	1.99 (1.62, 2.45), p<0.0001
FLC Ratio (>20 vs ≤20)	2.04 (1.65, 2.52), p<0.0001
BMPC (>20 vs ≤20)	2.26 (1.83, 2.79), p<0.0001

# Progression by risk group (n=1151 pts)



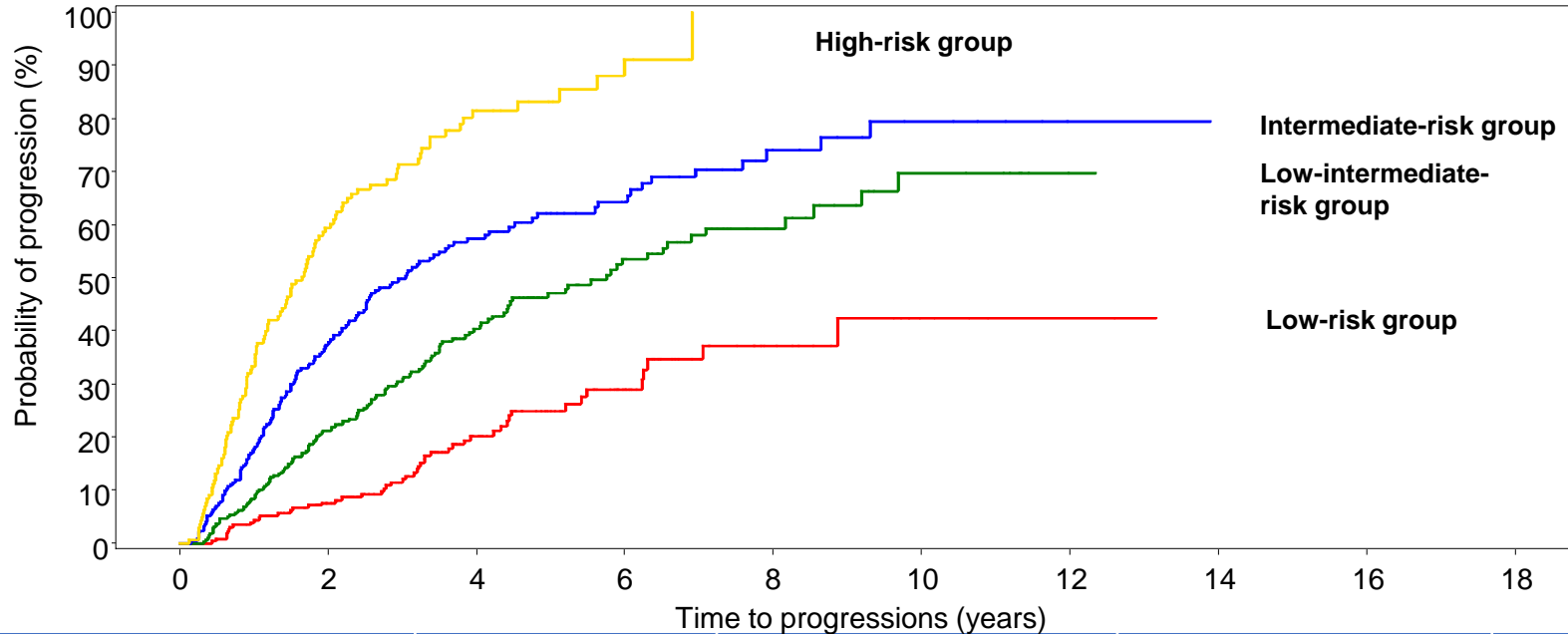
Characteristics included in the model

**Serum M Spike: >2 g/dL**  
**FLC Ratio: >20**  
**BMPC: >20%**

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
<b>Low-risk group</b>	<b>0</b>	Reference	<b>5%</b>	<b>424 (37%)</b>
<b>Intermediate-risk group</b>	<b>1</b>	2.25 (1.68 to 3.01)	<b>17%</b>	<b>312 (27%)</b>
<b>High-risk group</b>	<b>2-3</b>	5.63 (4.34 to 7.29)	<b>46%</b>	<b>415 (36%)</b>

# Progression risk incorporating FISH

-The presence of any four of **t(4,14)**, **t(14,16)**, **1q gain**, or **del13q** was defined as an additional risk factor



Characteristics included in the model

**Serum M Spike: >2 g/dL**

**FLC Ratio: >20**

**BMPC: >20%**

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
<b>Low-risk group</b>	<b>0</b>	Reference	<b>8%</b>	<b>232</b>
<b>Low-intermediate-risk group</b>	<b>1</b>	2.25 (1.62, 3.11)	<b>21%</b>	<b>322</b>
<b>Intermediate-risk group</b>	<b>2</b>	3.69 (2.68, 5.09)	<b>37%</b>	<b>253</b>
<b>High-risk group</b>	<b>&gt;=3</b>	7.52 (5.36, 10.54)	<b>59%</b>	<b>145</b>

# Modeling 2 year risk of progression

- **A logistic regression model**
- **Continuous variables categorized** based on clinical relevance as well visual trends in risk of progression (spline functions, odds ratio trends)
  - BMPC (0-15, >15-20, >20-30, >30-40, >40)
  - FLC (0-10, >10-25, >25-40, >40)
  - M Protein (0-1.5, >1.5-3, >3)
- **Scores for each risk factor were assigned as relative weights** of each coefficient in the multivariable regression model
- **Total risk score calculated as the sum of all points for all existing risk factors**
- For each risk score, the predicted risk can be approximated as:

$$p = 1 / [ 1 + e^{-(\text{intercept} + \text{riskscore} * \text{constant})} ]$$



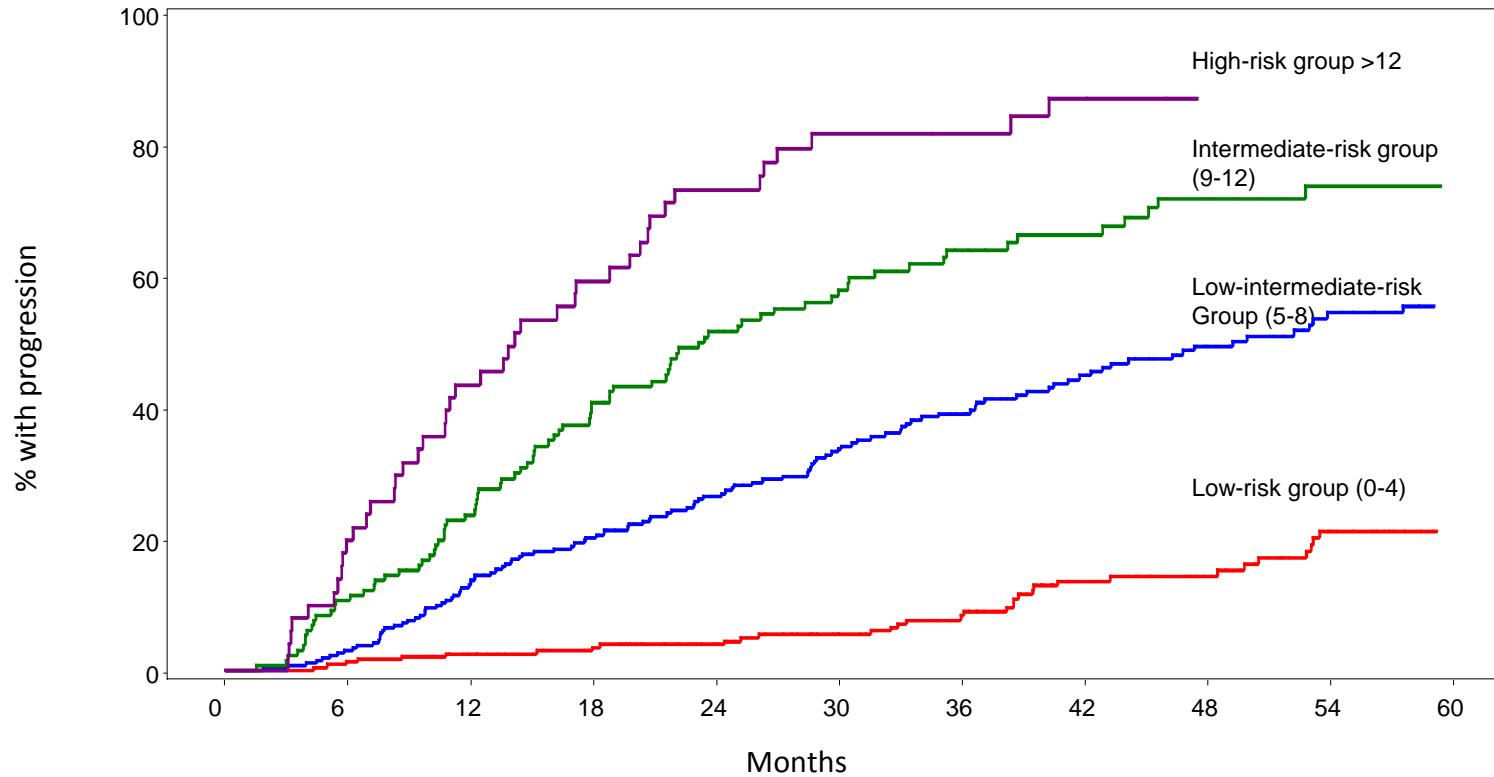
# Developing a Risk Score Tool (n=689 pts)

Risk Factor	Coefficient	Odds Ratio (95% CI)	P-value	Score
<b>FLC Ratio</b>				
0-10 (reference)	-	-	-	0
>10-25	0.69	1.99 (1.15, 3.45)	0.014	2
>25-40	0.96	2.61 (1.36, 4.99)	0.004	3
>40	1.56	4.73 (2.88, 7.77)	<0.0001	5
<b>M protein (g/dL)</b>				
0-1.5 (reference)	-	-	-	0
>1.5-3	0.95	2.59 (1.56, 4.31)	0.0002	3
>3	1.30	3.65 (2.02, 6.61)	<0.0001	4
<b>BMPC%</b>				
0-15 (reference)	-	-	-	0
>15-20	0.57	1.77 (1.03, 3.06)	0.04	2
>20-30	1.01	2.74 (1.6, 4.68)	0.0002	3
>30-40	1.57	4.82 (2.5, 9.28)	<0.0001	5
>40	2.00	7.42 (3.23, 17.02)	<0.0001	6
<b>FiSH abnormality</b>	0.83	2.28 (1.53, 3.42)	<0.0001	2

Total Risk score	Predicted risk at 2-years	% of sample
0	3.2	11.6
2	6.2	8.1
3	8.5	11.0
4	11.6	4.2
5	15.7	14.4
6	20.8	6.8
7	27	8.4
8	34.3	8.7
9	42.5	5.1
10	51	6.2
11	59.5	4.9
12	67.5	3.1
13	74.6	2.3
14	80.5	2.0
15	85.4	1.7
16+	89.2	1.3

\*689 of the original 2286 had complete data for all risk factors

# Progression risk



# at Risk	0	6	12	18	24	30	36	42	48	54	60
0-4	241	238	229	213	194	175	153	117	100	76	63
5-8	264	256	229	197	174	145	118	91	73	53	44
9-12	133	119	98	73	59	47	33	26	20	14	13
>12	51	41	29	21	14	9	7	5	2	2	2

Risk Stratification Groups	Hazard Ratio (95% CI) Versus Low-risk group (censored 2 year)
<b>0-4</b>	Reference
<b>5-8</b>	<b>7.56</b> (3.77 to 15.2)
<b>9-12</b>	<b>17.3</b> (8.63 to 34.8)
<b>&gt;12</b>	<b>31.9</b> (15.4 to 66.3)

Total Risk score	2 year progression n (%)
<b>0-4</b>	9 / 241 ( <b>3.7%</b> )
<b>5-8</b>	67 / 264 ( <b>25.4%</b> )
<b>9-12</b>	65 / 133 ( <b>48.9%</b> )
<b>&gt;12</b>	37 / 51 ( <b>72.6%</b> )

# Conclusions

- The 2/20/20 model is validated in the current analysis and potentially can be useful in circumstances where additional variables are not available
- Availability of FISH results can add to refining this system
- Ability to use the entire range of values for the risk factors allows for maximum utilization of the variables for calculating the risk of progression
- Risk scoring tool could be used to categorize individuals into low, medium, high risk depending on desired threshold. Scores  $< 5$  would give an 96% NPV (4% false negative), scoring tool only applicable up to 2-years.
- Alternate risk stratification systems may be used in individual trials, but whatever cutoff provides that 50% risk at 2 years is an acceptable patient population irrespective of the model used

# Acknowledgments

- To the IMWG and IMF for the support for doing this research
- To all investigators that collected the data to be analyzed
- Patients and their families